REMARKS

Claims 1-5, 9, 13, 14, 19-23, 27, 31, 32, and 37-44 were pending in this application. Claims 5, 9, 23, 27, 39, 40, 43, and 44 are cancelled without prejudice. Applicants expressly reserve the right to pursue protection of any or all of the subject matter of the cancelled claims in a subsequent application. Claims 1, 13, 14, 19, 31, 32, 37, 38, and 41 are amended. Support for the amending language of claims 1, 19 and 41 is found throughout the specification, specifically on page 19, line 28 to page 20, line 6 and on page 28, lines 26-30. Claims 13, 14, 31, and 32 have been amended to more clearly define what Applicants believe to be the scope of the invention. Claims 37 and 38 have been amended to change dependency. No new matter has been added by this amendment.

After entry of this amendment **claims 1-4, 13, 14, 19-22, 31, 32, 37, 38, 41, and 42 are pending in this application**. Consideration of the pending claims is respectfully requested.

Vacated Office Action and Information Disclosure Statement

The non-final Office action dated September 22, 2004 was vacated by the Examiner and replaced with the present non-final Office action. Attached to the vacated September 22, 2004 Office action was a form PTO-1449 listing 21 documents, each of which was initialed by the Examiner. Therefore, Applicants consider the documents to have been considered by the Examiner and of record. A copy of the form PTO-1449 is attached at the end of this response as Exhibit A.

Claim rejections under 35 U.S.C. § 103(a)

Claims 1-3, 5, 13, 14, 19-21, 23, 31, 32, 41, and 42 have been rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Kudlacz *et al.* (*Eur. J. Pharmacol.* 270:291-300, 1994) in view of Jafarian *et al.* (*Life Sciences* 57:143-53, 1995). Applicants respectfully traverse this rejection as applied to pending claims 1-3, 13, 14, 19-21, 31, 32, 41, and 42.

Kudlacz *et al.* discloses that substance P release occurs during periods of respiratory viral infection which are temporarily correlated with airway hyperresponsiveness, and that in conditions associated with tissue inflammation substance P levels are increased in associated fluids. Kudlacz *et al.* does not teach the administration of anti-substance P antibodies to a

subject, let alone the intranasal administration of anti-substance P antibody fragments to prevent/treat viral or bacterial-induced inflammation, or their use to reduce the levels of intracellular cytokines in a subject.

Jafarian *et al.* discloses that administration of a monoclonal anti-substance P antibody in guinea pigs can prevent the bronchospastic effects of exogenous substance P in these animals. Jafarian *et al.* does not teach the administration of anti-substance P **antibody fragments** to prevent/treat viral or bacterial-induced **inflammation**, or their use to reduce the levels of intracellular cytokines in a subject. The Office action contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kudlacz *et al.* and Jafarian *et al.* to treat viral induced airway inflammation and hyperresponsiveness by administration of anti-substance P antibodies.

The legal standard applicable to determinations of obviousness based on the prior art was reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art [citations omitted]. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** [emphasis added].

Therefore, three elements must be established in order to make a *prima facie* case of obviousness. First, the prior art must suggest, or provide the incentive for, the combination of references and/or their modification. Second, the combination and/or modification as suggested or motivated by the art must yield the process or invention claimed. Third, the prior art must provide a reasonable expectation of success of the claimed process. At no point may the Applicants' disclosure be used to satisfy any of the three elements. If any of these elements is absent, the obviousness rejection is unsupported.

In the present case, Applicants submit that no case of obviousness has been established. Nothing in Kudlacz *et al.*, which teaches substance P release during viral infection, suggests or provides motivation (either explicitly or implicitly) for combination with Jafarian *et al.* (or a

modification of its teachings), which teaches the use of anti-substance P antibodies to prevent/treat branchospastic effects of exogenous substance P and neurokinin A.

Moreover, even if this impermissible combination were made, one would not arrive at the claimed methods. Neither Jafarian *et al.* or Kudlacz et al. teach the administration of antibody fragments. In addition, neither Jafarian *et al.* or Kudlacz et al. teach ntranasal administration of anti-substance P **antibody fragments** to prevent/treat viral or bacterial-induced **inflammation**, or their use to reduce the levels of intracellular cytokines in a subject. Thus, Applicants submit that claims 1, 19 and 41, and claims depending therefrom (*i.e.*, claims 2, 3, 13, 14, 20, 21, 31, 32, and 42) are not obvious over Jafarian *et al.* or Kudlacz *et al.*

Moreover, the intranasal administration of $F(ab')_2$ anti-substance P antibody fragments provides an unexpectedly superior inhibition of inflammation as compared to the administration of intact anti-substance P antibodies. Submitted herewith is the Declaration of Ralph A. Tripp, which documents that naïve mice intranasally administered $F(ab')_2$ anti-substance P antibody fragments had reduced pulmonary inflammation (as indicated by reduced infiltration of macrophages, polymorphonuclear leukocytes, and eosinophils) as compared to mice intranasally administered intact anti-substance P antibodies. Thus, intranasal administration of anti-substance P antibody fragments resulted in an unexpectedly superior result in this mouse model system.

In light of the amendments to pending claims 1-3, 13, 14, 19-21, 31, 32, 41, and 42, the foregoing arguments, and Declaration, Applicants ask that the Examiner reconsider and withdraw this rejection of pending claims 1-3, 13, 14, 19-21, 31, 32, 41, and 42 under 35 U.S.C. § 103(a).

Claims 1-5, 13, 14, 19-23, 31, 32, 41, and 42 have been rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Kudlacz *et al.* in view of Jafarian *et al.* and Larsen (*Clin. Resp. Physiol.* 22:35-7, 1986). Applicants respectfully traverse this rejection as applied to pending claims 1-4, 13, 14, 19-22, 31, 32, 41, and 42.

Kudlacz *et al.* in view of Jafarian *et al.* are discussed above. As discussed above neither Kudlacz *et al.* nor Jafarian *et al.* disclose intranasal administration of anti-substance P **antibody fragments** to prevent/treat viral or bacterial-induced **inflammation**, or their use to reduce the levels of intracellular cytokines in a subject.

Larsen discloses that "insults" to the bronchial airways, such as infection by respiratory syncytial virus, result in inflammation and heightened reactivity. Larsen does not teach the use of $F(ab')_2$ anti-substance P antibody fragments, let alone the intranasal administration of these fragments.

The Office action contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kudlacz *et al.*, Jafarian *et al.* and Larsen to "treat substance P mediated inflammatory responses to respiratory syncytial virus" (page 4, paragraph 5). Applicants submit that the teachings of Larsen do not make up the deficiencies of Kudlacz *et al.* and Jafarian *et al.*

Moreover, as discussed above, the Declaration of Ralph A. Tripp documents that an unexpectedly superior reduction in inflammation was achieved when $F(ab')_2$ anti-substance P antibody fragments were intranasally administered to mice.

Thus, Applicants submit that claims 1-4, 13, 14, 19-22, 31, 32, 41, and 42 are not obvious over Kudlacz *et al.* and Jafarian *et al.* in combination with Larsen. Reconsideration and withdrawal of the rejection are respectfully submitted.

Claims 1-5, 9, 13, 14, 19-23, 27, 31, 32, 37, 38, 41, 42, and 44 have been further rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Kudlacz *et al.* in view of Jafarian *et al.* and U.S. Patent No. 5,256,766 (the '766 patent). Applicants respectfully traverse this rejection as applied to pending claims 1-4, 13, 14, 19-22, 31, 32, 37, 38, 41, and 42.

Kudlacz *et al.* and Jafarian *et al.* are discussed above.

The '766 patent discloses that the use of fragments (such as Fab and $F(ab')_2$) of antibodies that specifically bind **the thrombin receptor** can be used in a therapeutic context because these fragments are "generally less immunogenic" than the whole antibody. The '766 patent discloses that thrombin receptor antagonists, such as antibodies, can be administered by injection, such as intravenous, subcutaneous, intramuscular or intraperitoneal injection. Transmucosal and transdermal applications are also disclosed (see column 15, lines 35-45). The '766 patent further discloses that thrombin receptor antagonists can be administered topically, such as in the form of salves, pastes and gels (column 15, lines 60-64).

As discussed above, the prior art must suggest, or provide the incentive for, the combination of references and/or their modification. Applicants submit that nothing in the '766

patent which teaches antagonists to the thrombin receptor, either explicitly or implicitly suggests (or provides motivation) for combination with Kudlacz *et al.* and/or Jafarian *et al.*, which teach a role for substance P.

Moreover, even if this impermissible combination were made, one of skill in the art would not arrive at the claimed methods. None of Kudlacz *et al.*, Jafarian *et al.*, or the '766 patent discloses the intranasal administration of $F(ab')_2$ anti-substance P antibody fragments, let alone the intranasal administration of $F(ab')_2$ anti-substance P antibody fragments to prevent/treat viral or bacterial-induced inflammation, or to reduce the levels of intracellular cytokines in a subject. As discussed above, the Declaration of Ralph A. Tripp documents that an unexpectedly superior reduction in inflammation was achieved in a mouse model system using the intranasally administered $F(ab')_2$ anti-substance P antibody fragments.

Consequently, Applicants submit that neither Kudlacz *et al.*, Jafarian *et al.* nor the '766 patent, alone or in any combination, render obvious pending claims 1-4, 13, 14, 19-22, 31, 32, 37, 38, 41, and 42. Reconsideration and withdrawal of this rejection of pending claims 1-4, 13, 14, 19-22, 31, 32, 37, 38, 41, and 42 under 35 U.S.C. § 103(a) are respectfully requested.

Claims 1-3, 5, 13, 14, 19-21, 23, 31, 32, and 39-43 have been further rejected under 35 U.S.C. § 103(a), as being unpatentable over Kudlacz *et al.* in view of Jafarian *et al.* and U.S. Patent No. 6,034,105 (the '105 patent). Applicants respectfully traverse this rejection as applied to pending claims 1-3, 13, 14, 19-21, 31, 32, 41, and 42.

Kudlacz *et al.* and Jafarian *et al.* are discussed above.

The '105 patent discloses that "tacykinin antagonists" can be administered to a subject to alter its **circadian rhythm**. The '105 patent teaches the use of tacykinin antagonists that readily **penetrate the CNS** (column 7, lines 26-34). The disclosed tachykinin agonists are complex organic molecules and it is noted that non-peptidal agonists are preferred (see column 7, lines 25-29). The '105 patent discloses many routes of administration, including nasal administration (see column 32, lines 43-50).

The Office action contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kudlacz *et al.*, Jafarian *et al.* and the '105 patent to administer anti-substance P antibodies for treatment via an intraperitoneal route.

As discussed above, the prior art must suggest, or provide the incentive for, the combination of references and/or their modification. Applicants submit that nothing in Kudlacz *et al.* or Jafarian *et al.* that provides a motive to combine these references with the '105 patent, which teaches the administration of non-petidal agonists of tachykinin.

Moreover, even if this impermissible combination were made, one would not arrive at the Applicants invention. As discussed above, there is nothing in Kudlacz *et al.* or Jafarian *et al.* to suggests the intranasal administration of anti-substance P antibody fragments prevent/treat viral or bacterial-induced inflammation, or to reduce the levels of intracellular cytokines in a subject. Similarly, the '105 patent does not teach the administration of anti-substance P antibody fragments.

Moreover, the Declaration of Ralph A. Trip documents that *intranasal* delivery of $F(ab')_2$ anti-substance P antibody fragments provided an unexpectedly superior reduction of inflammation in naïve mice than another route of delivery, namely intraperitoneal delivery.

Consequently, Applicants submit that neither Kudlacz *et al.*, Jafarian *et al.* nor the '105 patent render obvious pending claims 1-3, 13, 14, 19-21, 31, 32, 41, and 42. Reconsideration and withdrawal of this rejection of pending claims 1-3, 13, 14, 19-21, 31, 32, 41, and 42 under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

Based on the foregoing, Applicants believe that pending claims 1-4, 13, 14, 19-22, 31, 32, 37, 38, 41, and 42 are in condition for allowance and notification to this effect is respectfully requested. The Examiner is invited to call the undersigned if the Examiner believes that a telephone interview would facilitate substantive examination of this application.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By _____
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Docket: 6395-59041	~~App: To be assigned~~
	Applicant: Tripp et al.	
	Filed: Herewith	Art Unit: ~~To be assigned~~ 1644

U.S. PATENT DOCUMENTS

Init.*		Number	Date	Name	Class	Sub	Filed
RV	1	4,419,352	Dec. 6, 1983	Cox et al.	—	—	
	2	5,332,817	Jul. 26, 1994	Desai et al.	—	—	
	3	5,340,822	Aug. 23, 1994	Emonds-Alt et al.	—	—	
	4	5,373,003	Dec. 13, 1994	Lowe, III	—	—	
	5	5,410,019	Apr. 25, 1995	Coy et al.	—	—	
	6	5,451,586	Sep. 19, 1995	Lowe, III	—	—	
	7	5,464,820	Nov. 7, 1995	Burton et al.	—	—	
	8	5,484,804	Jan. 16, 1996	Achard et al.	—	—	
	9	5,498,614	Mar. 12, 1996	Desai et al.	—	—	
	10	5,604,241	Feb. 18, 1997	Ito et al.	—	—	
	11	5,620,989	Apr. 15, 1997	Harrison et al.	—	—	
	12	5,688,806	Nov. 18, 1997	Desai et al.	—	—	

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RV	13	WO 92/16547	1 Oct. 1992	PCT	—	—		
	14	WO 96/29326	26 Sep. 1996	PCT	—	—		

OTHER DOCUMENTS

EXAMINER:	DATE 9/14/04

*Examiner: Initial if considered, whether or not in conformance with MPEP 609; draw line through cite if not in conformance and not considered. Send copy.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Docket: 6395-59041	~~App: To be assigned~~
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	Filed: Herewith	Art Unit: ~~To be assigned~~ 1644

RV	15		Agro et al., "Inhibition of Murine Intestinal Inflammation by Anti-Substance P Antibody," *Regional Immunology*, 5:120-126, 1993.
	16		Couraud et al., "Anti-substance P Anti-idiotypic Antibodies," *Journal of Biological Chemistry*, 260(16):9461-9469, 1985.
	17		Jafarian et al., "Passive Immunization with an Anti-Substance P Antibody Prevents Substance P-and Neurokin A-Induced Bronchospasm in Anesthetized Guinea-Pigs," *Life Sciences*, 57(2):143-153, 1995.
	18		Maillet et al., "Anti-substance P anti-idiotypic antibodies modulate the secretory process in the rat parotid gland in vitro," *European Journal of Pharmacology*, 187:357-367, 1990.
	19		Piccioli et al., Neuroantibodies: Ectopic Expression of a Recombinant Anti-Substance P Antibody in the Central Nervous System of Transgenic Mice," *Neuron*, 15:373-384, 1995.
	20		Swenberg et al., "Development of an anti-idiotypic antibody that blocks substance P primary antibodies and substance P membrane binding," *Brain Research*, 417:131-138, 1987.
	21		Tripp et al., "Respiratory Syncytial Virus Infection and G and/or SH Protein Expression Contribute to Substance P, Which Mediates Inflammation and Enhanced Pulmonary Disease in BALB/c Mice," *Journal of Virology*, 74(4):1614-1622, 2000.

EXAMINER:	DATE 9/14/04
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